REMARKS

Claims 97, 101-111 and 113-118 are pending in the application. Applicants have amended independent claims 97, 111 and 113 as shown above. These amendments are completely supported by the application as originally filed as demonstrated herein, and thus they do not raise any issue of new matter. Entry of this Amendment into the file of the application is respectfully requested since, for the reasons set forth below it is believed to place the claims of the application in condition for allowance, or at a minimum, to materially reduce the issues for an appeal.

Applicants appreciate the courtesies extended by Examiner Holleran during a telephone conference with their representative, Mark A. Farley (Reg. No. 33,170) on August 6, 2002. The remarks set forth herein are in accordance with the matters discussed during the subject telephone conference.

Applicants note with appreciation the statement in paragraph 3 on page 2 of the Office Action that the rejection of claims 97-99, 101-111, 113 and 115-118 under 35 U.S.C. 103(a) as being unpatentable over Livingston et al. (Cancer Research, 149:7045-7050, 1989) in view of Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Liane et al. (Journal of Biological Chemistry, 249 (14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (Immunobiol., 182:32-43, 1990), Kensil et al. (The Journal of Immunology, 146 (2):431-437, 1991), Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al. (J Biochem., 79 (6):1253-1261, 1976) is withdrawn in light of the amendments thereto.

Applicants additionally note the Examiner's statement in paragraph 4 on pages 2-3 of the Office Action that the rejection of claim 114 under 35 U.S.C. 103 (a) as being unpatentable over Livingston et al. (Cancer Research), Ritter et al. (Cancer Biology, 1991), Liane et al. (Journal of Biological Chemistry, 249 (14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (1990), Kensil et al., Marciani et al. And Uemera et al. (J Biochem., 79 (6):1253-1261, 1976) as applied to claims 97-99, 101-111, 113 and 115-118, and further in view of Irie et al. (U.S. Patent No. 4,557,931) is withdrawn in light of the amendments thereto.

Objection to the Disclosure

The Examiner stated that the prior objection to the disclosure is maintained for the reasons set forth in the Office Action mailed June 19, 1998 (Paper No. 16). The Examiner further stated that Applicants submit they will provide a new Figure 6B to overcome the rejection when the case is in condition for allowance. The Examiner additionally stated that until Applicants submit a proper Figure the objection is maintained.

In response, Applicants will provide a new Figure 6B upon the indication of allowable subject matter.

Obviousness Type Double Patenting Rejections

The Examiner stated that the rejection of claims 97, 101-111 and 113-118 as provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 78-92 and 94-99 of copending

Application No. 08/477,097 for the reasons made of record in Paper #20 mailed 10-6-1999, and Paper #22 mailed 6-27-2000 is maintained for the reasons of record, as Applicant(s) argues only that the rejection should be withdrawn if the claims are found allowable.

The Examiner also stated that the rejection of claims 97, 101-111 and 113-118 as provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending claims 78-93 and 95-100 of Application No. 08/475,084 [Sic, 08/475,784] for the reasons made of record in Paper #20 mailed 10-6-99, and Paper #22 mailed 6-27-2000 is maintained for reasons of record, as Applicant(s) argues only that the rejection should be withdrawn if the claims are found allowable.

The Examiner further stated that the rejection of claims 97, 101-111 and 113-118 as provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 109-122 of copending Application No. 08/477,147 is maintained for the reasons of record, as Applicant(s) argues only that the rejection should be withdrawn if the claims are found allowable. The Examiner went on to state that although the claims are not identical, they are not patentably distinct from each other because the claims of 08/477,147 also encompass the same composition as that which is instantly claimed (a conjugate comprising a ganglioside derivative with an altered ceramide portion conjugated to an immunogenic protein-based carrier, a saponin and a pharmaceutically acceptable carrier, and a method of treatment using such).

The above-described provisional double-patenting rejections are respectfully traversed. As noted by Applicants in their response filed April 12, 2002 to the previous Office Action concerning this application, M.P.E.P. section 804 IB, in discussing provisional double-patenting rejections between copending applications, requires that the:

> 'provisional' double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that 'provisional' double patenting rejection is the only rejection remaining in one of the applications. If the 'provisional' double patenting rejection in one application is the only rejection remaining in the application, the examiner should then withdraw the rejection and permit the application to issue as a patent, thereby converting the 'Provisional' double patenting rejection in the other application into a double patenting rejection at the time one application issues as a patent. (emphasis supplied by Applicants).

Applicants submit, therefore, for the reasons discussed below, that the claim amendments made hereto to claims 97, 111 and 113 are believed to overcome the 35 U.S.C. 112, paragraphs 1 and 2, rejection of those claims, as well as the claims which depend therefrom, which rejections should therefore be withdrawn. Following such withdrawal of the section 112 rejections, the only remaining rejections in this application would be the provisional double patenting rejections. In accordance with the M.P.E.P. section quoted above, therefore,

the provisional double patenting rejections should thus be withdrawn to permit this application to issue as a patent. Such action is therefore respectfully solicited.

NEW GROUNDS OF REJECTION

Rejection Under 35 U.S.C. 112, Second Paragraph:

The Examiner stated, in paragraph 10 on page 5 of the Office Action, that claims 97, 101-111 and 113-118 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant(s) regard as the invention. The Examiner additionally stated with regard to this rejection that the claims refer to a C-4 carbon of the sphingosine base of the ceramide portion of the ganglioside derivative, which clearly is drawn to the starting compounds from which the claimed conjugate is formed, and that later the claim recites that the C-4 carbon is present in a CH_2 group, which clearly refers to the final formed conjugate. The Examiner further stated that it is thus not clear if the C-4 carbon referred to is part of the starting materials (as part of the ganglioside derivative) or part of the ultimate conjugate product. The Examiner additionally stated that amending the claim so that the C-4 carbon is consistently referred to in terms of it's position in the ultimate conjugate would likely bring favorable consideration.

Rejection Under 35 U.S.C. 112, First Paragraph:

The Examiner stated, in paragraph 12 on pages 5-6 of the Office Action, that claims 97, 101-111 and 113-118 are additionally rejected under 35 U.S.C. 112, first paragraph, as

containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner stated that the claims now recite that the C-4 carbon is present in a CH_2 group. The Examiner stated that the Applicants do not cite a portion of the specification which provides support for this limitation. The Examiner went on to state that the claims appear to find support for this specific configuration in Figure 1. The Examiner went on to state, however, that the claim as recited encompasses molecules other than that depicted in Figure 1 and that Figure 1 is a species of the genus of molecules claimed. The Examine stated that it is not clear that the specification as filed specifically contemplated the generic composition instantly claimed, which has the specific limitation that the C-4 carbon is present in a CH_2 group. The Examiner also stated that because there is no support in the specification for a compound as instantly claimed, with a C-4 carbon present as part of a CH_2 group, this limitation is new matter as it is different from the scope of any of the compounds initially contemplated. The Examiner stated further that limiting the claims to the compound of Figure 1, or making it clear where in the specification provides support for this specific limitation in terms of the generic claim will likely bring favorable consideration.

Response To Rejections Under 35 U.S.C. 112:

Applicants respectfully traverse the rejections under 35 U.S.C. 112, paragraphs 1 and 2, for the reasons below. In response to these rejections, Applicants have amended claims 97, 111 and 113, i.e., all of the independent claims present

in the application, to further clarify the mode of conjugation between the ganglioside derivative and the Keyhole Limpet Hemocyanin, while deleting the phrase, "[w]herein the C-4 carbon is present in a CH_2 group." More particularly, the subject independent claims, as now amended, recite that in the conjugate the ganglioside derivative is covalently bound to Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the altered sphingosine base of the altered ceramide portion of the ganglioside derivative and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin. The amendments to the independent claims are clearly supported, as explained below, by the following portions of the specification taken in combination with one another: Figure 1; page 5, lines 4-7; page 32, lines 13-20; and page 65, lines 9-15.

More specifically, the specification at page 5, lines 4-5, states that Figure 1 illustrates the synthesis of GD3 protein conjugates after ozone cleavage and reductive amination. The Examiner notes, however, as indicated above, that Figure 1 is a species of the genus of molecules claimed, that is, that Figure 1 illustrates a conjugate incorporating a different ganglioside, i.e., GD3, than the GM2 ganglioside which is recited in the present claims. Applicants understand the Examiner's remarks to mean that the specific example illustrated in Figure 1 would not provide sufficient support for a claim directed to the inclusion, in the claimed conjugate, of a derivative of a ganglioside <u>other than</u> GD3, i.e., such as the GM2 ganglioside which is specifically recited in Applicants' claims.

The Examiner's attention is respectfully directed, however, to page 32 of the specification which teaches, at lines 15-20,

concerning the conjugation of the GD3 ganglioside to a protein, that:

> The ceramide, characteristic for all gangliosides, was cleaved with ozone at the C-4 position of the sphingosine base and a functional aldehyde group was introduced. Coupling to proteins was realized by reductive amination to form a stable amine bond between ganglioside and ε-aminolysyl groups of proteins.

The above-described mode of conjugation was not used, however, solely to conjugate the GD3 ganglioside. Its universality for use in conjugating the other ganglioside derivatives contemplated for use with Applicants' invention, particularly the GM2 ganglioside specifically recited in Applicants' claims, is demonstrated, for example, by the text at page 65, lines 9-15 of the specification which, in describing the preparation of a GM2-Keyhole Limpet Hemocyanin vaccine, i.e., incorporating GM2 instead of GD3 as the ganglioside, teaches that:

> GM2-KLH conjugate was prepared ... as described previously for GD3-KLH conjugate vaccine. Briefly, the conjugation procedure involved ozone cleavage of the ceramide double bond of GM2, introduction of an aldehyde group, and conjugation of aminolysyl groups of KLH by reductive amination.

In summary, therefore, pages 5 and 32 of the specification, taken together with Figure 1, clearly disclose to one of ordinary skill in this art the conjugation of a GD3 ganglioside derivative to an immunogenic protein based carrier

(i.e., KLH) by a stable amine bond between the C-4 carbon of the altered sphingosine base of the altered ceramide portion of the ganglioside derivative and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin. Further, page 32 of the specification describes the ceramide moiety of the GD3 ganglioside as being, "[c]haracteristic for all gangliosides." Moreover, page 65 of the specification goes on to teach that the same mode of conjugation used with GD3 is also used with the GM2 ganglioside.

Taken together, therefore, the cited portions of the specification clearly demonstrate that Applicants had possession of the invention, as presently claimed, at the time the application was filed. The Examiner's rejection under 35 U.S.C. 112, first paragraph, is therefore believed to have been overcome and thus should be withdrawn.

Moreover, with regard to the rejection under 35 U.S.C. 112, second paragraph, Applicants submit that the amendments to the independent claims make it very clear to one of ordinary skill in this art that the bond referred to in the subject claims is that found in the final formed conjugate. These amendments are thus believed to overcome the rejection of the subject claims under the second paragraph of section 112, which should also be withdrawn.

Further, the rejections of the claims which depend from the independent claims are also believed to have been overcome, for the same reasons as the rejections of the independent claims. Withdrawal of the rejections to the dependent claims is thus also respectfully solicited.

Summary

For all of the reasons set forth above, Applicants respectfully request that the Examiner reconsider and withdraw the various grounds for rejection and earnestly solicit allowance of the pending claims, nos. 97, 101-111 and 113-118.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' attorneys invite the Examiner to telephone at the number provided below.

No fee is believed to be due with this submission. However, if any fee is due, authorization is hereby provided to charge the required amount due to Deposit Account No. 03-3125.

Respectfully submitted,

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EXHIBIT A

Applicants: Philip O. Livingston and Friedhelm Helling
Serial No.: 08/196,154
Filed : November 16, 1995
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EXHIBIT A

AMENDED CLAIMS

In the Claims:

Please amend claims 97, 111, and 113 as follows:

--97. (3x amended) A composition which comprises:

a) a conjugate of i) a GM2 ganglioside derivative which comprises an unaltered oligosaccharide part and an altered ceramide portion comprising [a] an altered sphingosine base, to ii) Keyhole Limpet Hemocyanin, comprising an ε-aminolysyl group;

b) a saponin derivable from the bark of a Quillaja saponaria Molina tree; and

c) a pharmaceutically acceptable carrier;

the relative amounts of such conjugate and such saponin being effective to stimulate or enhance antibody production in a subject,
wherein in the conjugate the ganglioside derivative is covalently bound to Keyhole Limpet Hemocyanin by a stable amine bond between the [through a] C-4 carbon of the altered sphingosine base of the altered ceramide portion of the ganglioside derivative [to] and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin [wherein the C-4 carbon is present in a CH_2 group].--

--111. (3x amended) A method of stimulating or enhancing antibody production in a subject which comprises administering to the subject an effective amount of a composition which comprises:

a) a conjugate of i) a GM2 ganglioside derivative which comprises an unaltered oligosaccharide part and an altered ceramide portion comprising [a] an altered sphingosine base, to ii) Keyhole Limpet Hemocyanin comprising an ε-aminolysyl group;

b) a saponin derivable from the bark of a Quillaja saponaria Molina tree; and

c) a pharmaceutically acceptable carrier;

the relative amounts of such conjugate and such saponin being effective to stimulate or enhance antibody production in a subject,
wherein in the conjugate the ganglioside derivative is covalently bound to Keyhole Limpet Hemocyanin by a stable amine bond between the [through a] C-4 carbon of the altered sphingosine base of the altered ceramide portion of the ganglioside derivative [to] and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin [, wherein the C-4 carbon is present in a CH_2 group], so as to thereby stimulate or enhance antibody production in the subject.--

--113. (3x amended) A method of treating a cancer in a subject which comprises administering to the

subject an effective cancer treating amount of a composition which comprises:

a) a conjugate of i) a GM2 ganglioside derivative which comprises an unaltered oligosaccharide part and an altered ceramide portion comprising [a] an altered sphingosine base, to ii) Keyhole Limpet Hemocyanin comprising an ε-aminolysyl group;

b) a saponin derivable from the bark of a Quillaja saponaria Molina tree; and

c) a pharmaceutically acceptable carrier;

the relative amounts of such conjugate and such saponin being effective to stimulate or enhance antibody production in a subject,
wherein in the conjugate the ganglioside derivative is covalently bound to Keyhole Limpet Hemocyanin by a stable amine bond between the [through a] C-4 carbon of the altered sphingosine base of the altered ceramide portion of the ganglioside derivative [to] and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin [, wherein the C-4 carbon is present in a CH_2 group], so as to thereby treat the cancer in the subject.--